IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SANOFI-AVENTIS and SANOFI-AVENTIS U.S. LLC, Plaintiffs, vs. ACTAVIS SOUTH ATLANTIC LLC, AUROBINDO PHARMA LTD., AUROBINDO PHARMA USA INC., MYLAN PHARMACEUTICALS INC., PAR PHARMACEUTICAL, INC., RANBAXY INC., RANBAXY LABORATORIES LIMITED, SUN PHARMACEUTICAL INDUSTRIES, INC., SUN PHARMACEUTICAL INDUSTRIES LTD, TEVA PHARMACEUTICALS USA, INC., TORRENT PHARMA INC. and TORRENT PHARMACEUTICALS LIMITED, Defendants.	C.A. No. _____

COMPLAINT

Plaintiffs sanofi-aventis and sanofi-aventis U.S. LLC ("sanofi-aventis U.S."), for their Complaint against Defendants Actavis South Atlantic LLC ("Actavis"), Aurobindo Pharma Ltd. ("Aurobindo Ltd."), Aurobindo Pharma USA Inc. ("Aurobindo Inc."), Mylan Pharmaceuticals Inc. ("Mylan"), Par Pharmaceutical, Inc. ("Par"), Ranbaxy Inc., Ranbaxy Laboratories Limited ("Ranbaxy Ltd."), Sun Pharmaceutical Industries, Inc. ("Sun Inc."), Sun Pharmaceutical Industries Ltd. ("Sun Ltd."), Teva Pharmaceuticals USA, Inc. ("Teva"), Torrent Pharma Inc. ("Torrent Inc.") and Torrent Pharmaceuticals Ltd. ("Torrent Ltd."), hereby allege as follows:

Parties

1. Plaintiff sanofi-aventis is a corporation organized and existing under the laws of France, having its principal place of business at 174 avenue de France, Paris, France 75013.

2. Plaintiff sanofi-aventis U.S. is a limited liability company organized and existing under the laws of Delaware with its North American headquarters located at 55 Corporate Drive, Bridgewater, New Jersey 08807.

3. Upon information and belief, Defendant Actavis is a Delaware limited liability company having a place of business at 13800 NW 2nd Street, Ste-190, Fort Lauderdale, Florida 33325.

4. Upon information and belief, Defendant Aurobindo Inc. is a Delaware corporation, and the wholly-owned subsidiary and agent of Defendant Aurobindo Ltd., having a place of business at 2400 Route 130 North, Dayton, New Jersey 08810.

5. Upon information and belief, Defendant Aurobindo Ltd. is an Indian corporation having a place of business at Plot No. 2, Maitri Vihar, Ameerpet, Hyderabad – 500 038, Andhra Pradesh, India. Upon information and belief, Defendant Aurobindo Ltd. manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, through its wholly-owned subsidiary and agent Aurobindo Inc.

6. Upon information and belief, Defendant Mylan is a West Virginia corporation having a place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia, 26504. Upon information and belief, Defendant Mylan manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

7. Upon information and belief, Defendant Par is a Delaware corporation having a place of business at 300 Tice Boulevard, Woodcliff Lake, New Jersey 07677.

8. Upon information and belief, Defendant Ranbaxy Inc. is a Delaware corporation, and the wholly-owned subsidiary and agent of Defendant Ranbaxy Ltd., having a place of business at 600 College Road East, Princeton, New Jersey 08540.

9. Upon information and belief, Defendant Ranbaxy Ltd. is an Indian corporation having a place of business at Plot 90, Sector 32, Gurgaon -122001 (Haryana), India. Upon information and belief, Defendant Ranbaxy Ltd. manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, through its wholly-owned subsidiary and agent Defendant Ranbaxy Inc.

10. Upon information and belief, Defendant Sun Inc. was a Michigan corporation, and the wholly-owned subsidiary and agent of Defendant Sun Ltd., having a place of business at 29714 Orion CT, Farmington Hills, Michigan 48334 at the time it submitted its Abbreviated New Drug Application. Upon information and belief, Sun Inc. dissolved as a corporation on or about July 15, 2007. Upon information and belief, Defendant Sun Inc. manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

11. Upon information and belief, Defendant Sun Ltd. is an Indian corporation having a place of business at Acme Plaza, Andheri - Kurla Rd, Andheri (E), Mumbai - 400 059. Upon information and belief, Defendant Sun Ltd., itself and through its wholly-owned subsidiary and agent Defendant Sun Inc., manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

12. Upon information and belief, Defendant Teva is a Delaware corporation having a place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454.

13. Upon information and belief, Defendant Torrent Inc. is a Delaware corporation, and the wholly-owned subsidiary and agent of Defendant Torrent Ltd., having a place of business at 3585 Bellflower Drive, Portage, Michigan 49024.

14. Upon information and belief, Defendant Torrent Ltd. is an Indian company having a place of business at Torrent House, Off Ashram Road, Ahmedabad - 380 009, Gujarat, India. Upon information and belief, Defendant Torrent Ltd. manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, through its wholly-owned subsidiary and agent Defendant Torrent Inc.

Nature of the Action

15. This is a civil action for the infringement of United States Patent No. 4,661,491 ("the '491 patent") (Exhibit A) and United States Patent No. 6,149,940 ("the '940 patent") (Exhibit B). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*

Jurisdiction and Venue

16. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

17. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to a Delaware company, Plaintiff sanofi-aventis U.S. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

18. This Court has personal jurisdiction over Defendant Actavis by virtue of the fact that, *inter alia*, Actavis is a Delaware limited liability company.

19. This Court has personal jurisdiction over Defendant Aurobindo Inc. by virtue of the fact that, *inter alia*, Aurobindo Inc. is a Delaware corporation.

20. This Court has personal jurisdiction over Defendant Aurobindo Ltd. by virtue of, *inter alia*: (1) its presence in Delaware through its subsidiary and agent Aurobindo Inc.; and (2) its systematic and continuous contacts with Delaware, including through its subsidiary and agent Aurobindo Inc.

21. This Court has personal jurisdiction over Defendant Mylan by virtue of, *inter alia*, its systematic and continuous contacts with Delaware.

22. This Court has personal jurisdiction over Defendant Par by virtue of the fact that, *inter alia*, Par is a Delaware corporation.

23. This Court has personal jurisdiction over Defendant Ranbaxy Inc. by virtue of the fact that, *inter alia*, Ranbaxy Inc. is a Delaware corporation.

24. This Court has personal jurisdiction over Defendant Ranbaxy Ltd. by virtue of, *inter alia*: (1) its presence in Delaware through its subsidiary and agent Ranbaxy Inc.; and (2) its systematic and continuous contacts with Delaware, including through its subsidiary and agent Ranbaxy Inc.

25. This Court has personal jurisdiction over Defendant Sun Inc. by virtue of, *inter alia*, its systematic and continuous contacts with Delaware.

26. This Court has personal jurisdiction over Defendant Sun Ltd. by virtue of, *inter alia*, its systematic and continuous contacts with Delaware, including through its subsidiary and agent Sun Inc.

27. This Court has personal jurisdiction over Defendant Teva by virtue of the fact that, *inter alia*, Teva is a Delaware corporation.

28. This Court has personal jurisdiction over Defendant Torrent Inc. by virtue of the fact that, *inter alia*, Torrent Inc. is a Delaware corporation.

29. This Court has personal jurisdiction over Defendant Torrent Ltd. by virtue of, *inter alia*: (1) its presence in Delaware through its subsidiary and agent Torrent Inc.; and (2) its systematic and continuous contacts with Delaware, including through its subsidiary and agent Torrent Inc.

30. Venue is proper in this judicial district as to each defendant pursuant to 28 U.S.C. §§ 1391 and 1400(b).

The Patents

31. On April 28, 1987, the '491 patent, titled "Alfuzosine Compositions and Use," was duly and legally issued by the United States Patent and Trademark Office ("PTO"). Plaintiff sanofi-aventis is the current assignee of the '491 patent. Plaintiff sanofi-aventis U.S. holds New Drug Application ("NDA") No. 21-287 on Uroxatral® brand alfuzosin hydrochloride extended release tablets, and is the exclusive distributor of Uroxatral® in the United States. The '491 patent is listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book") for Uroxatral®.

32. On November 21, 2000, the '940 patent, titled "Tablet with Controlled Release of Alfuzosine Chlorhydrate," was duly and legally issued by the PTO. Plaintiff sanofi-aventis and Jagotec AG are the current assignees of the '940 patent. Plaintiff sanofi-aventis has an exclusive license to Jagotec AG's interests in the '940 patent. Pursuant to that license, sanofi-aventis has the right to unilaterally bring and proceed with this action in its own name. Jagotec has also consented to sanofi-aventis bringing this action. The '940 patent is listed in the Orange Book for Uroxatral®.

Acts Giving Rise to this Action

Count I – Infringement of the '491 Patent by Defendants Actavis and Par

33. Upon information and belief, Actavis submitted Abbreviated New Drug Application ("ANDA") 79-055 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). That ANDA seeks FDA approval for the commercial manufacture, use, offer for sale and sale of generic extended release tablets containing 10 mg of alfuzosin hydrochloride per tablet. ANDA 79-055 specifically seeks FDA approval to market a proposed generic version of sanofi-aventis' Uroxatral® brand alfuzosin hydrochloride 10 mg tablet product prior to the expiration of the '491 patent.

34. Actavis alleged in ANDA 79-055 under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '491 patent are invalid. Plaintiffs received written notification of ANDA 79-055 on or about August 17, 2007.

35. Actavis' submission of ANDA 79-055 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '491 patent under 35 U.S.C. § 271(e)(2)(A). Actavis' commercial use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '491 patent.

36. Par is jointly and severally liable for Actavis' infringement of the '491 patent. Upon information and belief, Par participated in, contributed to, aided, abetted and/or induced Actavis' submission of ANDA 79-055 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

37. Par's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 79-055 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '491 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, Par's

commercial manufacture, use, offer for sale or sale of the proposed generic versions of sanofi-aventis' Uroxatral® brand product would infringe the '491 patent.

38. This is an exceptional case under 35 U.S.C. § 285 because Actavis and Par were aware of the existence of the '491 patent at the time of the submission of ANDA 79-055 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA and that filing constituted infringement of the '491 patent.

39. Plaintiffs will be irreparably harmed by Defendant Actavis' and Defendant Par's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

Count II – Infringement of the '940 Patent by Defendants Actavis and Par

40. ANDA 79-055 specifically seeks FDA approval to market a proposed generic version of sanofi-aventis' Uroxatral® brand alfuzosin hydrochloride 10 mg tablet product prior to the expiration of the '940 patent.

41. Actavis has alleged in ANDA 79-055 under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '940 patent are not infringed by the manufacture, use or sale of the proposed generic version of sanofi-aventis' Uroxatral® brand product. Plaintiffs received written notification of ANDA 79-055 on or about August 17, 2007.

42. Actavis' submission of ANDA 79-055 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '940 patent under 35 U.S.C. § 271(e)(2)(A). Actavis' commercial use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '940 patent.

43. Par is jointly and severally liable for Actavis' infringement of the '940 patent. Upon information and belief, Par participated in, contributed to, aided, abetted and/or

induced Actavis' submission of ANDA 79-055 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

44. Par's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 79-055 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '940 patent under 35 U.S.C. § 271(e)(2)(A). Par's commercial manufacture, use, offer for sale or sale of its proposed generic versions of sanofi-aventis' Uroxatral® brand product would infringe the '940 patent.

45. This is an exceptional case under 35 U.S.C. § 285 because Actavis and Par were aware of the existence of the '940 patent at the time of the submission of ANDA 79-055 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA and that filing constituted infringement of the '940 patent.

46. Plaintiffs will be irreparably harmed by Defendant Actavis' and Defendant Par's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

Count III – Infringement of the '491 Patent by Defendants Aurobindo Ltd. and Aurobindo Inc.

47. Upon information and belief, Aurobindo Ltd., through its subsidiary and agent Aurobindo Inc., submitted ANDA 79-060 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). That ANDA seeks FDA approval for the commercial manufacture, use, offer for sale and sale of generic extended release tablets containing 10 mg of alfuzosin hydrochloride per tablet. ANDA 79-060 specifically seeks FDA approval to market a proposed generic version of sanofi-aventis' Uroxatral® brand alfuzosin hydrochloride 10 mg tablet product prior to the expiration of the '491 patent.

48. Aurobindo Ltd. alleged in ANDA 79-060 under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '491 patent are invalid or not infringed by the manufacture, use or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product. Plaintiffs received written notification of ANDA 79-060 on or about August 30, 2007.

49. Aurobindo Ltd.'s submission of ANDA 79-060 to the FDA, through Aurobindo Inc., including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '491 patent under 35 U.S.C. § 271(e)(2)(A). Aurobindo Ltd.'s commercial use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '491 patent.

50. Aurobindo Inc. is jointly and severally liable for Aurobindo Ltd.'s infringement of the '491 patent. Upon information and belief, Aurobindo Inc. participated in, contributed to, aided, abetted and/or induced Aurobindo Ltd.'s submission of ANDA 79-060 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

51. Aurobindo Inc.'s participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 79-060 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '491 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, Aurobindo Inc.'s commercial manufacture, use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '491 patent.

52. This is an exceptional case under 35 U.S.C. § 285 because Aurobindo Ltd. and Aurobindo Inc. were aware of the existence of the '491 patent at the time of the submission of ANDA 79-060 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA and that filing constituted infringement of the '491 patent.

53. Plaintiffs will be irreparably harmed by Defendant Aurobindo Ltd.'s and Defendant Aurobindo Inc.'s infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

Count IV – Infringement of the '940 Patent by Defendants Aurobindo Ltd. and Aurobindo Inc.

54. ANDA 79-060 specifically seeks FDA approval to market a proposed generic version of sanofi-aventis' Uroxatral® brand alfuzosin hydrochloride 10 mg tablet product prior to the expiration of the '940 patent.

55. Aurobindo Ltd. alleged in ANDA 79-060 under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '940 patent are invalid or not infringed by the manufacture, use or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product. Plaintiffs received written notification of ANDA 79-060 on or about August 30, 2007.

56. Aurobindo Ltd.'s submission of ANDA 79-060 to the FDA, through Aurobindo Inc., including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '940 patent under 35 U.S.C. § 271(e)(2)(A). Aurobindo Ltd.'s commercial use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '940 patent.

57. Aurobindo Inc. is jointly and severally liable for Aurobindo Ltd.'s infringement of the '940 patent. Upon information and belief, Aurobindo Inc. participated in, contributed to, aided, abetted and/or induced Aurobindo Ltd.'s submission of ANDA 79-060 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

58. Aurobindo Inc.'s participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 79-060 and its § 505(j)(2)(A)(vii)(IV) allegations to the

FDA constitutes infringement of the '940 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, Aurobindo Inc.'s commercial manufacture, use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '940 patent.

59. This is an exceptional case under 35 U.S.C. § 285 because Aurobindo Ltd. and Aurobindo Inc. were aware of the existence of the '940 patent at the time of the submission of ANDA 79-060 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA and that filing constituted infringement of the '940 patent.

60. Plaintiffs will be irreparably harmed by Defendant Aurobindo Ltd.'s and Defendant Aurobindo Inc.'s infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

Count V – Infringement of the '491 Patent by Defendant Mylan

61. Upon information and belief, Mylan submitted ANDA 79-014 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). That ANDA seeks FDA approval for the commercial manufacture, use, offer for sale and sale of generic extended release tablets containing 10 mg of alfuzosin hydrochloride per tablet. ANDA 79-014 specifically seeks FDA approval to market a proposed generic version of sanofi-aventis' Uroxatral® brand alfuzosin hydrochloride 10 mg tablet product prior to the expiration of the '491 patent.

62. Mylan alleged in ANDA 79-014 under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '491 patent are invalid. Plaintiffs received written notification of ANDA 79-014 on or about August 27, 2007.

63. Mylan's submission of ANDA 79-014 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '491 patent under 35 U.S.C.

§ 271(e)(2)(A). Mylan's commercial use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '491 patent.

64. This is an exceptional case under 35 U.S.C. § 285 because Mylan was aware of the existence of the '491 patent at the time of the submission of ANDA 79-014 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA and that filing constituted infringement of the '491 patent.

65. Plaintiffs will be irreparably harmed by Defendant Mylan's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

Count VI – Infringement of the '940 Patent by Defendant Mylan

66. ANDA 79-014 specifically seeks FDA approval to market a proposed generic version of sanofi-aventis' Uroxatral® brand alfuzosin hydrochloride 10 mg tablet product prior to the expiration of the '940 patent.

67. Mylan alleged in ANDA 79-014 under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '940 patent are not infringed by the manufacture, use or sale of the proposed generic version of sanofi-aventis' Uroxatral® brand product. Plaintiffs received written notification of ANDA 79-014 on or about August 27, 2007.

68. Mylan's submission of ANDA 79-014 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '940 patent under 35 U.S.C. § 271(e)(2)(A). Mylan has provided limited information related to its proposed generic version of sanofi-aventis' Uroxatral® brand product that is the subject of ANDA 79-014. However, given Mylan's claim of bioequivalence contained within ANDA 79-014, Plaintiffs believe that they are likely to have evidentiary support after a reasonable opportunity for further investigation

or discovery that will demonstrate that Mylan's commercial use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand would infringe the '940 patent.

69. This is an exceptional case under 35 U.S.C. § 285 because Mylan was aware of the existence of the '940 patent at the time of the submission of ANDA 79-014 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA and that filing constituted infringement of the '940 patent.

70. Plaintiffs will be irreparably harmed by Defendant Mylan's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

Count VII – Infringement of the '940 Patent by Defendants Ranbaxy Ltd. and Ranbaxy Inc.

71. Upon information and belief, Ranbaxy Ltd., through its subsidiary and agent Ranbaxy Inc., submitted ANDA 79-006 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). That ANDA seeks FDA approval for the commercial manufacture, use, offer for sale and sale of generic extended release tablets containing 10 mg of alfuzosin hydrochloride per tablet. ANDA 79-006 specifically seeks FDA approval to market a proposed generic version of sanofi-aventis' Uroxatral® brand alfuzosin hydrochloride 10 mg tablet product prior to the expiration of the '940 patent.

72. Ranbaxy Ltd. alleged in ANDA 79-006 under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '940 patent are not infringed by the manufacture, use or sale of the proposed generic version of sanofi-aventis' Uroxatral® brand product. Plaintiffs received written notification of ANDA 79-006 on or about August 14, 2007.

73. Ranbaxy Ltd.'s submission of ANDA 79-006 to the FDA, through Ranbaxy Inc., including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the

'940 patent under 35 U.S.C. § 271(e)(2)(A). Ranbaxy Ltd.'s commercial use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand would infringe the '940 patent.

74. Ranbaxy Inc. is jointly and severally liable for any infringement of the '940 patent. Upon information and belief, Ranbaxy Inc. participated in, contributed to, aided, abetted and/or induced Ranbaxy Ltd.'s submission of ANDA 79-006 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

75. Ranbaxy Inc.'s participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 79-006 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '940 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, Ranbaxy Inc.'s commercial manufacture, use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '940 patent.

76. This is an exceptional case under 35 U.S.C. § 285 because Ranbaxy Ltd. and Ranbaxy Inc. were aware of the existence of the '940 patent at the time of the submission of ANDA 79-006 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA and that filing constituted infringement of the '940 patent.

77. Plaintiffs will be irreparably harmed by Defendant Ranbaxy Ltd.'s and Defendant Ranbaxy Inc.'s infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

Count VIII – Infringement of the '940 Patent by Defendants Sun Inc. and Sun Ltd.

78. Upon information and belief, Sun Inc. acting as a subsidiary and agent of Sun Ltd., submitted ANDA 79-057 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 79-057 seeks FDA approval for the commercial manufacture, use, offer for sale and sale of generic extended release tablets containing 10 mg of

alfuzosin hydrochloride per tablet. ANDA 79-057 specifically seeks FDA approval to market a proposed generic version of sanofi-aventis' Uroxatral® brand alfuzosin hydrochloride 10 mg tablet product prior to the expiration of the '940 patent.

79. Sun Inc. alleged in ANDA 79-057 under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '940 patent are not infringed by the manufacture, use or sale of the proposed generic version of sanofi-aventis' Uroxatral® brand product. Plaintiffs received written notification of ANDA 79-057 on or about September 6, 2007.

80. Sun Inc.'s submission of ANDA 79-057 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '940 patent under 35 U.S.C. § 271(e)(2)(A). Sun Inc. has provided no information related to its proposed generic version of sanofi-aventis' Uroxatral® brand product that is the subject of ANDA 79-057. However, given Sun Inc.'s claim of bioequivalence contained within ANDA 79-057, Plaintiffs believe that they are likely to have evidentiary support after a reasonable opportunity for further investigation or discovery that will demonstrate that Sun Inc.'s commercial use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand would infringe the '940 patent.

81. Sun Ltd. is jointly and severally liable for Sun Inc.'s infringement of the '940 patent. Upon information and belief, Sun Ltd. participated in, contributed to, aided, abetted and/or induced Sun Inc.'s submission of ANDA 79-057 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

82. Sun Ltd.'s participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 79-057 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '940 patent under 35 U.S.C. § 271(e)(2)(A). Sun Ltd.'s

commercial manufacture, use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '940 patent.

83. This is an exceptional case under 35 U.S.C. § 285 because Sun Inc. and Sun Ltd. were aware of the existence of the '940 patent at the time of the submission of ANDA 79-057 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA and that filing constituted infringement of the '940 patent.

84. Plaintiffs will be irreparably harmed by Defendant Sun Inc.'s and Defendant Sun Ltd.'s infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

Count IX – Infringement of the '491 Patent by Defendant Teva

85. Upon information and belief, Teva submitted ANDA 79-056 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). That ANDA seeks FDA approval for the commercial manufacture, use, offer for sale and sale of generic extended release tablets containing 10 mg of alfuzosin hydrochloride per tablet. ANDA 79-056 specifically seeks FDA approval to market a proposed generic version of sanofi-aventis' Uroxatral® brand alfuzosin hydrochloride 10 mg tablet product prior to the expiration of the '491 patent.

86. Teva alleged in ANDA 79-056 under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '491 patent are invalid or not infringed by the manufacture, use or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product. Plaintiffs received written notification of ANDA 79-056 on or about August 15, 2007.

87. Teva's submission of ANDA 79-056 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '491 patent under 35 U.S.C.

§ 271(e)(2)(A). Teva's commercial use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '491 patent.

88. This is an exceptional case under 35 U.S.C. § 285 because Teva was aware of the existence of the '491 patent at the time of the submission of ANDA 79-056 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA and that filing constituted infringement of the '491 patent.

89. Plaintiffs will be irreparably harmed by Defendant Teva's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

Count X – Infringement of the '940 Patent by Defendant Teva

90. ANDA 79-056 specifically seeks FDA approval to market a proposed generic version of sanofi-aventis' Uroxatral® brand alfuzosin hydrochloride 10 mg tablet product prior to the expiration of the '940 patent.

91. Teva alleged in ANDA 79-056 under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '940 patent are not infringed by the manufacture, use or sale of the proposed generic version of sanofi-aventis' Uroxatral® brand product. Plaintiffs received written notification of ANDA 79-056 on or about August 15, 2007.

92. Teva's submission of ANDA 79-056 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '940 patent under 35 U.S.C. § 271(e)(2)(A). Teva has provided limited information related to its proposed generic version of sanofi-aventis' Uroxatral® brand product that is the subject of ANDA 79-056. However, given Teva's claim of bioequivalence contained within ANDA 79-056, Plaintiffs believe that they are likely to have evidentiary support after a reasonable opportunity for further investigation or

discovery that will demonstrate that Teva's commercial use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand would infringe the '940 patent.

93. This is an exceptional case under 35 U.S.C. § 285 because Teva was aware of the existence of the '940 patent at the time of the submission of ANDA 79-056 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA and that filing constituted infringement of the '940 patent.

94. Plaintiffs will be irreparably harmed by Defendant Teva's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

Count XI – Infringement of the '491 Patent by Defendants Torrent Ltd. and Torrent Inc.

95. Upon information and belief, Torrent Ltd., through its subsidiary and agent Torrent Inc., submitted ANDA 79-054 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). That ANDA seeks FDA approval for the commercial manufacture, use, offer for sale and sale of generic extended release tablets containing 10 mg of alfuzosin hydrochloride per tablet. ANDA 79-054 specifically seeks FDA approval to market a proposed generic version of sanofi-aventis' Uroxatral® brand alfuzosin hydrochloride 10 mg tablet product prior to the expiration of the '491 patent.

96. Torrent Ltd. alleged in ANDA 79-054 under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '491 patent are invalid. Plaintiffs received written notification of ANDA 79-054 on or about August 16, 2007.

97. Torrent Ltd.'s submission of ANDA 79-054 to the FDA, through Torrent Inc., including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '491 patent under 35 U.S.C. § 271(e)(2)(A). Torrent Ltd.'s commercial use, offer for sale or sale of its

proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '491 patent.

98. Torrent Inc. is jointly and severally liable for any infringement of the '491 patent. Upon information and belief, Torrent Inc. participated in, contributed to, aided, abetted and/or induced Torrent Ltd.'s submission of ANDA 79-054 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

99. Torrent Inc.'s participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 79-054 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '491 patent under 35 U.S.C. § 271(e)(2)(A). Torrent Inc.'s commercial manufacture, use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '491 patent.

100. This is an exceptional case under 35 U.S.C. § 285 because Torrent Ltd. and Torrent Inc. were aware of the existence of the '491 patent at the time of the submission of ANDA 79-054 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA and that filing constituted infringement of the '491 patent.

101. Plaintiffs will be irreparably harmed by Defendant Torrent Ltd.'s and Defendant Torrent Inc.'s infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

Count XII – Infringement of the '940 Patent by Defendants Torrent Ltd. and Torrent Inc.

102. ANDA 79-054 specifically seeks FDA approval to market a proposed generic version of sanofi-aventis' Uroxatral® brand alfuzosin hydrochloride 10 mg tablet product prior to the expiration of the '940 patent.

103. Torrent Ltd. alleged in ANDA 79-054 under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '940 patent are invalid and not

infringed by the manufacture, use or sale of the proposed generic version of sanofi-aventis' Uroxatral® brand product. Plaintiffs received written notification of ANDA 79-054 on or about August 16, 2007.

104. Torrent Ltd.'s submission of ANDA 79-054 to the FDA, through Torrent Inc., including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '940 patent under 35 U.S.C. § 271(e)(2)(A). Torrent Ltd.'s commercial use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand would infringe the '940 patent.

105. Torrent Inc. is jointly and severally liable for Torrent Ltd.'s infringement of the '940 patent. Upon information and belief, Torrent Inc. participated in, contributed to, aided, abetted and/or induced the submission of ANDA 79-054 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

106. Torrent Inc.'s participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 79-054 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '940 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, Torrent Inc.'s commercial manufacture, use, offer for sale or sale of its proposed generic version of sanofi-aventis' Uroxatral® brand product would infringe the '940 patent.

107. This is an exceptional case under 35 U.S.C. § 285 because Torrent Ltd. and Torrent Inc. were aware of the existence of the '940 patent at the time of the submission of ANDA 79-054 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA and that filing constituted infringement of the '940 patent.

108. Plaintiffs will be irreparably harmed by Defendant Torrent Ltd.'s and Defendant Torrent Inc.'s infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

Prayer for Relief

WHEREFORE, Plaintiffs pray for judgment as follows:

A. That Defendants Actavis, Aurobindo Ltd., Aurobindo Inc., Mylan, Par, Teva, Torrent Inc. and Torrent Ltd. have infringed the '491 patent;

B. That all Defendants have infringed the '940 patent;

C. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Defendants' ANDAs identified in this Complaint shall not be earlier than the expiration dates of the '491 patent and '940 patent, including any extensions;

D. That Defendants Actavis, Aurobindo Ltd., Aurobindo Inc., Mylan, Par, Teva, Torrent Ltd. and Torrent Inc., their officers, agents, servants and employees, and those persons in active concert or participation with any of them, be preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, or selling the proposed generic versions of sanofi-aventis' Uroxatral® brand product identified in this Complaint, and any other product that infringes or induces or contributes to the infringement of the '491 patent, prior to the expiration of the '491 patent, including any extensions;

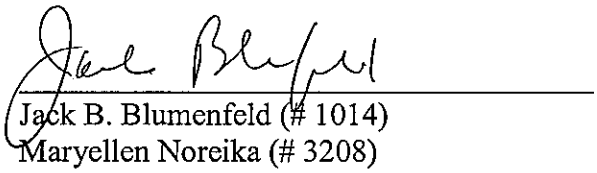
E. That Defendants, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, be preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, or selling the proposed generic versions of sanofi-aventis' Uroxatral® brand product identified in this Complaint, and any other product that infringes or induces or contributes to the infringement of the '940 patent, prior to the expiration of the '940 patent, including any extensions;

F. That this case is exceptional under 35 U.S.C. § 285;

G. That Plaintiffs be awarded the attorney fees, costs and expenses that they incur prosecuting this action; and

H. That Plaintiffs be awarded such other and further relief as this Court deems just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP



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Dated: September 21, 2007

EXHIBIT A

United States Patent [19]

Regnier

[11] **Patent Number: 4,661,491**

[45] **Date of Patent: Apr. 28, 1987**

[54] **ALFUZOSINE COMPOSITIONS AND USE**

[75] Inventor: **François Regnier**, Nancy, France

[73] Assignee: **Synthelabo**, Paris, France

[21] Appl. No.: **867,031**

[22] Filed: **May 27, 1986**

[30] **Foreign Application Priority Data**

May 28, 1985 [FR] France 85 07950

[51] **Int. Cl.**[4] **A61K 31/505**

[52] **U.S. Cl.** **514/260**

[58] **Field of Search** 514/260

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,315,007 2/1982 Manoury 514/259

Primary Examiner—Allen J. Robinson

Attorney, Agent, or Firm—Wegner & Bretschneider

[57] **ABSTRACT**

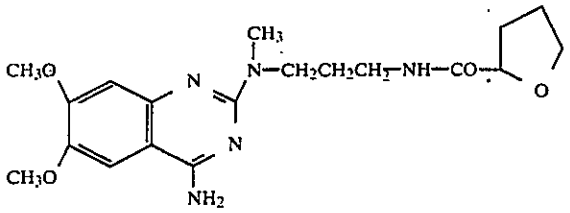
A method for treating humans or non-human animals for dysuria comprising administering an effective non-toxic amount of alfuzosine or a pharmaceutically acceptable salt thereof to a human or non-human animal suffering dysuria.

5 Claims, No Drawings

ALFUZOSINE COMPOSITIONS AND USE

The present invention relates to pharmaceutical compositions containing alfuzosine and the use of alfuzosine in the treatment of dysuria.

Alfuzosine, the compound of formula



is known for its antihypertensive activity. It is an antagonist of vascular α_1-adrenergic receptors which possesses direct muscle-relaxant properties.

In many patients manifesting dysuria, an exceptionally high cervico-urethral pressure is observed, which is related to a relative hyperactivity of the α-adrenergic receptors.

It has now been found that alfuzosine has activitity in altering the phenylephrine-induced contractions on preparations of smooth muscle originating from the base of the bladder (trigone muscle) and the urethra of rabbits and that alfuzosine can be used for the treatment of conditions of the lower urinary apparatus, in which hyperactivity of the alpha-adrenergic receptors of the vesicosphincter system disturbs the continence/micturition cycle.

Accordingly the present invention provides a method for treating dysuria in humans or non-human animals comprising administering a therapeutic amount of alfuzosine or a pharmaceutically acceptable salt thereof to a human or animal suffering dysuria.

Patients who may be treated are, for example, men and women who have bladder neck disease, or men who have benign hypertrophy of the prostrate with dysuria of alpha-adrenergic origin.

Other patients who may be treated include those suffering from neurological disorders such as paraplegia or multiple sclerosis, for whom the disturbance of micturition also responds to alfuzosine.

The daily dosage can range from 0.5 to 10 mg for adult humans.

The present invention also provides a pharamceutical composition for treating dysuria comprising an effective amount of alfuzosine or a pharmaceutically acceptable salt thereof and a pharmaceutical diluent or carrier therefor.

The pharmaceutical compositions of the invention containing alfuzosine or a pharmaceutically acceptable salt thereof in combination with any suitable excipient can be administered orally, parenterally or transdermally. They are presented in any suitable form such as gelatine capsules, tablets, solutions, and the like. The pharmaceutical compositions can also be presented in the form of delayed-release tablets or gelatine capsules.

The pharmaceutically acceptable salts include acid addition salts of a pharamceutically acceptable organic or inorganic acid such as mineral acids and mono-, di- or tri- carboxylic acids, especially the hydrochloride salt.

The invention will now be illustrated by the following Pharmacological Data and Formulation Examples.

PHARMACOLOGICAL DATA

Male rabbits (CEGAN) weighing 3 to 4 kg are sacrificed by exsanguination and cervical dislocation.

The bladder and urethra are rapidly removed and placed in lukewarm Krebs solution containing bicarbonate.

The composition of this Krebs medium is as follows, in mM: NaCl 114; KCl 4.7; $CaCl_2$ 2.5; KH_2PO_4 1.2; $MgSO_4$ 1.2; $NaHCO_3$ 25.0; glucose 11.7; ascorbic acid 1.1. Propranolol (1.0 μM) is added into the Krebs medium to block the β-adrenergic receptors.

The bladder is opened transversely and the "trigone" region of the muscle, located on the dorsal surface of the bladder and between the two ureters, is dissected out.

A 5 mm ring of urethra, from the region situated between the base of the bladder and the prostate, is also prepared.

The portions of trigone muscle and urethra are washed under a tension of 1 g in Krebs medium.

The contraction-response curve to cumulated concentrations of phenylephrine is determined.

Additions of the agonist are performed every 5 min. The tissues are washed until the original tension is reestablished, and are then incubated for 30 min with alfuzosine. A second response curve to phenylephrine is determined in the presence of alfuzosine.

The response curves to concentrations of phenylephrine in the presence or absence of alfuzosine are expressed as a percentage of the maximum response obtained relative to the control curve.

The power of alfuzosine is calculated in the form of pA_2 by Schild's method, where pA_2=negative logarithm of the molar concentration of alfuzosine which causes a rightward shift of the response curve to the agonist.

Alfuzosine (at a dose of 3.0 μM) causes a significant rightward parallel shift of the response curve to phenylephrine both in the trigone muscle and in the urethra. Alfuzosine causes a 20 to 30% reduction in the maximum contractile effects of phenylephrine.

By Schild analysis, the pA_2 can be determined, this being 7.05-0.17.

By means of clinical studies, it has also been possible to show the efficacy of alfuzosine in patients suffering from dysuria of neurological origin with urethral hypertonia.

5 mg of alfuzosine are injected intravenously continuously for a period of 20 min. Sphincterometric measurements were made using an electronic micro-sensor, before and after the injection of the drug, at the bladder neck and at the striated sphincter of the posterior urethra.

The results of these measurements enabled a 44% pressure decrease ($p<0.001$) to be noted at the bladder neck, and a 39% decrease ($p<0.001$) at the striated sphincter.

A clinical study was also performed in paraplegics.

The paraplegic, or spinal man, gives rise to an experimental model of the peripheral receptors, since he embodies a disconnection from the influence of the higher, diencephalic and cortical nerve centres.

Given the localization of the alpha-adrenergic receptors in the posterior urethra and the vesico-urethral segment or neck, alpha-adrenergic hypertonia is the

source of dysuria and disturbances of micturition. The opening of the neck and the fall in the pressure gradient in the posterior urethra are the two conditions required for the production of effective micturition.

Alfuzosine was administered intravenously, and then orally if the first test is positive. 5 mg of alfuzosine are injected intravenously in the course of 20 min.

After injection of alfuzosine, the intra-urethral pressures decrease significantly. The test is considered to be positive if an initiation of micturition, that is to say, necessarily, opening of the neck, takes place.

For patients for whom the test is positive, the administration of alfuzosine was then performed orally at the rate of 9 mg/24 h/28 d.

In most cases, the treatment per os enabled micturition to be rendered easier to initiate.

FORMULATION EXAMPLES

Examples of pharmaceutical formulations are given below:

	mg
Tablet:	
Alfuzosine (as the hydrochloride salt)	5
Microcrystalline cellulose	36
Lactose	122
Sodium carboxymethylamide	7
Polyvidone excipient	9
Magnesium stearate	1
	180
Coating env.	8
Injectable Solution	
Alfuzosine (as the hydrochloride salt)	1
Sodium chloride	44.9
Water for injection qs	5 ml

I claim:

1. A method for treating humans or non-human animals for dysuria comprising administering an effective dysuria controlling, non-toxic amount of alfuzosine or a pharmaceutically acceptable salt thereof to a human or non-human animal suffering dysuria.

2. A method according to claim 1 comprising administering alfuzosine hydrochloride.

3. A method according to claim 1 comprising administering from 0.5 to 10 mg of alfuzosine or the corresponding amount of a pharmaceutically acceptable salt thereof.

4. A method according to claim 1 for treating dysuria in patients having bladder neck disease or a neurological disorder.

5. A method according to claim 1 for treating dysuria in male patients having benign hypertrophy of the prostrate of alpha-adrenergic origin.

* * * * *

EXHIBIT B

US006149940A

United States Patent [19]

Maggi et al.

[11] Patent Number: 6,149,940

[45] Date of Patent: Nov. 21, 2000

[54] **TABLET WITH CONTROLLED RELEASE OF ALFUZOSINE CHLORHYDRATE**

[75] Inventors: **Lauretta Maggi**, Pavia; **Ubaldo Conte**, Busto Arisizio., both of Italy; **Pascal Grenier**; **Guy Vergnault**, both of Saint Louis, France; **Alain Dufour**, Paris, France; **François Xavier Jarreau**, Versailles, France; **Clemence Rauch-Desanti**, Ozoire la Ferrière, France

[73] Assignees: **Synthelabo**, Le Plessis-Robinson, France; **Jagotec AB**, Hergiswil, Switzerland

[21] Appl. No.: **09/147,581**

[22] PCT Filed: **Aug. 22, 1997**

[86] PCT No.: **PCT/FR97/01515**

§ 371 Date: **Apr. 26, 1999**

§ 102(e) Date: **Apr. 26, 1999**

[87] PCT Pub. No.: **WO98/08515**

PCT Pub. Date: **Mar. 5, 1998**

[30] **Foreign Application Priority Data**

Aug. 29, 1996 [FR] France 96 10551
Apr. 10, 1997 [FR] France 97 04386

[51] **Int. Cl.**[7] **A61K 9/24**; A61K 9/28; A61K 9/22

[52] **U.S. Cl.** **424/472**; 424/468; 424/474; 514/772.3; 514/777; 514/778; 514/779; 514/773; 514/781; 514/784; 514/785

[58] **Field of Search** 424/468, 469, 424/470, 472, 474, 465

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,661,491	4/1987	Regnier	514/260
4,839,177	6/1989	Colombo et al.	424/482
5,422,123	6/1995	Conte et al.	424/479
5,589,190	12/1996	Andrieu et al.	424/462

FOREIGN PATENT DOCUMENTS

WO94/27582 12/1994 WIPO .

Primary Examiner—James M. Spear
Attorney, Agent, or Firm—Jacobson, Price, Holman & Stern, PLLC

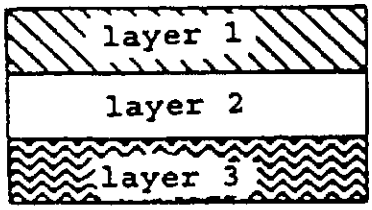
[57] **ABSTRACT**

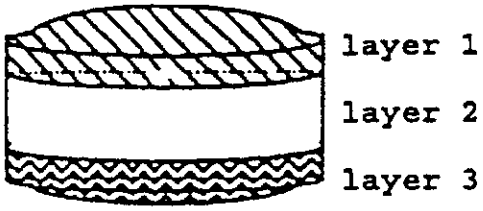
Pharmaceutical tablet which consists of:

a) a first layer having the property of swelling considerably and quickly on contact with aqueous biological fluids, the first layer being produced by compression of a mixture or of a granulate comprising hydrophilic polymers, and

b) a second layer adjacent to the first layer being formulated with hydrophilic polymers and with other auxiliary substances in order to give the preparation suitable properties of compressibility and in order to allow the release of alfuzosin hydrochloride within a predetermined time period.

23 Claims, 2 Drawing Sheets





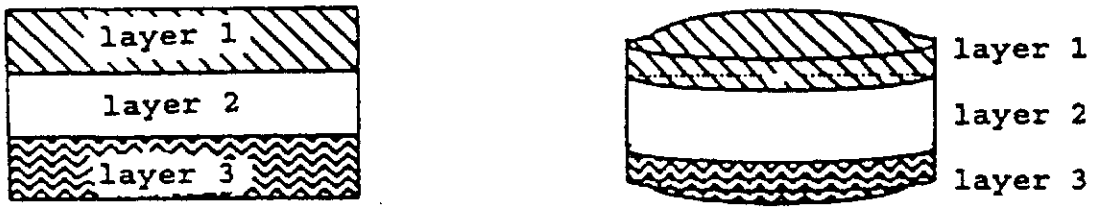


Fig. 1

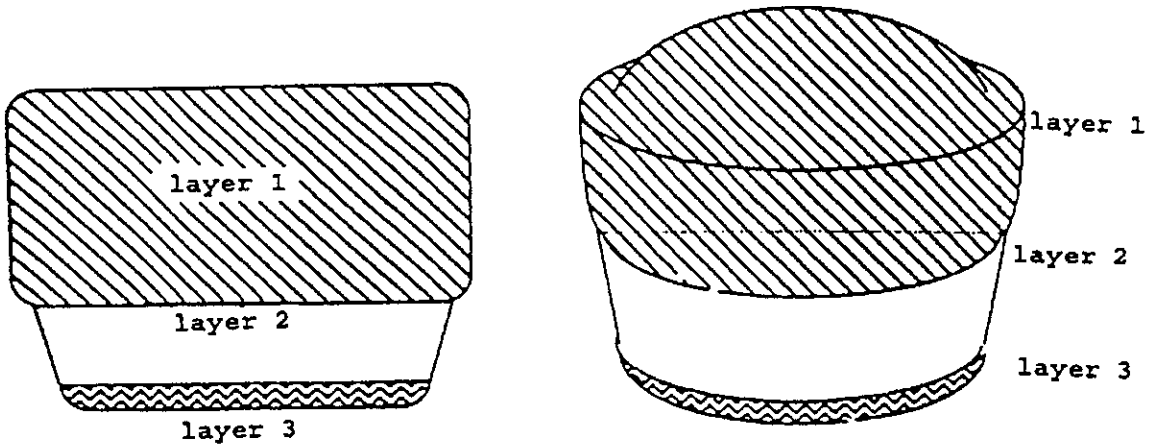


Fig. 2

TABLET WITH CONTROLLED RELEASE OF ALFUZOSINE CHLORHYDRATE

This applicatin is a 371 of PCT/FR97/01515 filed Aug. 27, 1997.

The present invention relates to a tablet with controlled release of alfuzosin hydrochloride and to a pharmaceutical composition containing one or more tablets.

Alfuzosin hydrochloride is an active substance that is known in the treatment of benign hypertrophy of the prostate. There is a wealth of data and experimental studies regarding the activity of the product. In particular, there is a large amount of data regarding the bioavailability of the product and the pharmacokinetics of the active substance. Indeed, it is an active substance which has a relatively short half-life and a more intense absorption at the duodenum-jejunum level, but the size of which decreases along the intestinal tract. Consequently, for an optimum effect, the administration of alfuzosin hydrochloride as conventional tablets (with rapid disintegration and dissolution) must be carried out several times a day. For these reasons, alfuzosin hydrochloride is a candidate for the production of a pharmaceutical preparation with controlled release in the promixal upper parts of the tract (duodenum and jejunum).

In the pharmaceutical field, noteworthy progress has been made in recent years in the production of increasingly improved systems for the release of active substances, which are capable of releasing the active substances conveyed per se according to kinetics and modes of release designed to allow optimum therapeutic effects.

Prolonged-release forms (or delayed-effect preparations) are characterized in that they convey a markedly larger amount of medicinal product than traditional pharmaceutical preparations, so as to allow the dosage to be simplified. That is to say that the administration decreases from two, three or more times a day to only one administration of a pharmaceutical preparation (or therapeutic system) capable of providing satisfactory therapeutic cover throughout the day.

Preparations of this type have been used and marketed for a long time, among which mention should be made of: chronoids, microcapsules and micro-matrices, tablets generically defined as "delayed-effect" tablets, gastro-resistent tablets and more complex preparations such as hydrophilic matrices which break down and/or swell. Recently, more refined therapeutic systems have been produced, for example so-called "reservoir" systems and the Geomatrix® systems as described in U.S. Pat. Nos. 4,839,177 and 5,422,123.

Most of these novel therapeutic systems are capable of releasing the active substance conveyed per se, at a constant rate (that is to say according to zero-order kinetics) up to complete release of the active substance, independently of the pH conditions of the gastrointestinal tract, and thus uniformly along the gastrointestinal tract. It results therefrom that these systems may be applied widely in the case of administration of medicinal products that are absorbed uniformly in the gastrointestinal tract. However, these pharmaceutical systems may have major drawbacks in the case where active substances per se would be conveyed, such as alfuzosin, having a more intense absorption at the duodenum-jejunum level which decreases thereafter in the tract. Indeed, in this case, only a very limited amount of the active substance conveyed may be absorbed and thus exert the desired therapeutic activity, whereas most of the medicinal product released by the pharmaceutical preparation cannot be absorbed since, in lower portions of the gastrointestinal tract, the biological barriers are relatively incapable of allowing the medicinal product to pass.

The subject of the present patent application is a tablet with controlled release of alfuzosin hydrochloride, which overcomes the drawbacks mentioned above.

The invention consists of a pharmaceutical tablet containing two or three layers, characterized in that it has the following structure:

a) a first layer **1** having the property of swelling considerably and quickly on contact with aqueous biological fluids, the said layer being produced by compression of a mixture or of a granulate comprising hydrophilic polymers constituting from 5.0 to 90% and preferably from 10 to 85% of the weight of the layer,

b) a second layer **2** adjacent to the first layer, in which the alfuzosin hydrochloride is conveyed, this layer being formulated with hydrophilic polymers and with other auxiliary substances, in order to give the preparation suitable properties of compressibility and in order to allow the release of alfuzosin hydrochloride within a predetermined time period,

c) and optionally a third layer **3** obtained by compression and applied to the layer **2**, generally consisting in particular of hydrophilic polymers which gel and/or swell and which may then optionally be broken down and having a barrier function which modifies the release of the alfuzosin hydrochloride from the layer **2**, the layer **3** being primarily highly impervious to passage of the active substance.

The invention is characterized in that on contact with gastric juices, after rapid and considerable swelling of at least one of the layers **1** or **3**, as well as by the possible swelling of the layer **2**, the pharmaceutical preparation increases considerably in volume; thus, the pharmaceutical preparation remains in the stomach for longer. In this way, most of the alfuzosin hydrochloride contained may be absorbed in a controlled manner in that portion of the gastrointestinal tract which has the highest capacity for absorption.

The layers **1** and **3** may have an identical composition and identical functional properties or they may have a different composition and different properties.

When the layers **1** and **3** have identical functional properties and compositions, they may differ by their amounts and their thicknesses applied to the layer **2**.

At least one of the layers **1** and **3** acts as a barrier, that is to say that it is primarily highly impervious to passage of the alfuzosin hydrochloride contained in the layer **2** and at least one of the layers is characterized in that it swells quickly, that is to say that it quickly increases in volume.

Another embodiment of the pharmaceutical preparation is characterized in that the tablet containing **3** layers is formed of a first layer **1** as described above, that is to say that its sole function is to increase considerably in volume on contact with aqueous liquids, a second layer **2** conveying some of the alfuzosin hydrochloride which has to be released within a predetermined time period, and a third layer **3** in which some of the alfuzosin hydrochloride is conveyed, formulated such that it can be released immediately on contact with gastric juices.

The amount of alfuzosin hydrochloride carried in the tablet is between 2.5 and 50 mg.

The polymeric substances which are used in the layers **1** and **3**, and which may also be used in the layer **2**, are biocompatible and have hydrophilic properties. They are slowly soluble and/or slowly gelable and/or swell rapidly or at a different rate in aqueous liquids and then may optionally be broken down; they are chosen from the following group: hydroxymethylcellulose, hydroxyethyl-cellulose, hydroxypropylmethylcellulose having a molecular weight of

from 1000 to 4,000,000, hydroxypropylcellulose having a molecular weight of from 2000 to 2,000,000, carboxyvinyl polymers, chitosans, mannans, galactomannans, xanthans, carrageenans, amylose, alginic acid, its salts and its derivatives, pectins, acrylates, methacrylates, acrylic/methacrylic copolymers, polyanhydrides, polyamino acids, poly(methyl vinyl ether/maleic anhydride) polymers, polyvinyl alcohols, glucans, scleroglucans, carboxymethylcellulose and its derivatives, ethylcellulose, methylcellulose and, in general, hydrophilic cellulose derivatives.

The content of hydrophilic polymers may range from 5 to 90% relative to the total weight of the layer, but preferably from 10 to 85% and more particularly from 20 to 80%.

In order to promote a rapid and considerable increase in the volume of the pharmaceutical preparation, during the preparation of the layers **1** and **3**, with the hydrophilic polymers mentioned above, it is possible to use hydrophilic products and/or excipients capable of promoting wetting of the layers, in this way facilitating interaction between the components of the said layer and the biological fluids with which the layer comes into contact. These hydrophilic excipients are preferably chosen from the groups of so-called "super disintegrating" excipients comprising crosslinked polyvinylpyrrolidone, hydroxypropylcellulose and hydroxypropylmethylcellulose having a molecular weight form 1,000 to 100,000, crosslinked sodium carboxymethylcellulose, carboxymethyl starch and its salts, and divinylbenzene/potassium methacrylate copolymer.

These substances constitute from 1 to 50% of the weight of the layer and preferably from 10 to 30%.

It is moreover possible also to use surfactants (anionic, cationic and nonionic surfactants) which, by facilitating wetting, allow a more rapid interaction between the dissolution medium (or gastric fluid) and the tablet, thereby allowing much faster wetting and swelling of the pharmaceutical preparation, preferably of the layer in which this hydration-modifying component is conveyed. In the group of substances possessing these properties, mention may be made of products such as sodium lauryl sulphate, sodium ricinoleate, sodium tetradecyl sulphate, sodium dioctyl sulphosuccinate, cetomagrogol, poloxamer, glyceryl monostearate, polysorbates, sorbitan monolaurate, lecithins or any other pharmaceutically acceptable surfactant.

In addition, other hydration-modifying elements may be used, these being chosen from the following group of substances:

- hydrophilic diluents such as mannitol, lactose, starches of various origins, sorbitol, xylitol, microcrystalline cellulose and/or substances which, in general, promote the penetration of water or of aqueous fluids into the pharmaceutical preparation,
- hydrophobic diluents such as glyceryl monostearate, palmitates, hydrogenated or unhydrogenated plant oils such as hydrogenated castor oil, waxes, mono-, di- or trisubstituted glycerides, for slowing down the penetration of water or of aqueous fluids into the pharmaceutical preparation.

The technical preparation of the tablets may lead to introducing:

- lubricants such as magnesium stearate, stearic acid, glyceryl monostearate, polyoxyethylene glycols having a molecular weight of from 400 to 7,000,000, hydrogenated castor oil, glyceryl behenate, mono-, di- or trisubstituted glycerides,
- flow agents such as colloidal silica or any other silica,
- and binders, buffers, absorbing agents, as well as any other pharmaceutically acceptable additive.

The tablets of the invention may be produced in the following way: powders and/or granulates are mixed using current production technologies and thus with a production process which may be industrialized immediately.

The pharmaceutical tablet containing two or three layers is obtained according to tableting processes that are very commonly used and known to those skilled in the art.

For example, the tablets may be produced using rotary presses capable of producing "multi-layer" tablets.

Normally, the working compression force ranges from 7 to 50 KN (or kilonewtons) and, according to the processes which will be described in greater detail in the examples, tablets containing two or three layers having a cylindrical, lenticular, spheroidal or ovoid shape which makes them easy to administer and to swallow, are obtained.

Depending on the amount of active substance which is conveyed, each layer of the tablet may have a different thickness ranging from 0.2 to 8 mm, but preferably from 1 mm to 4 mm.

A coating made of polymer materials, whose aim is to afford simple protection or alternatively a slowing-down at the start of the release of the active substance conveyed in the pharmaceutical preparation, may also be applied to this pharmaceutical prepartion. The coating may be soluble in acidic solution or alternatively permeable, so t activation of the tablet (release of the active substance) only after a predetermined time period.

According to another embodiment of the invention, a soluble coating containing alfuzosin hydrochloride may be applied so as to allow immediate release of some of the active substance on contact with the gastric juices.

The coating may be applied by standard methods known to those skilled in the art using organic or aqueous solutions.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** presents an embodiment of the invention comprising a tablet with three layers as described above.

On contact with gastric juices and/or fluids of the gastrointestinal tract, the tablet rapidly increases in volume, taking the structure shown in FIG. **2**.

This increase in volume may be determined and limited to a single layer or to several layers of the tablet; this increase in volume, as well as the rate at which this phenomenon takes place, may be monitored and evaluated precisely by direct measurement or by a video microscope coupled to a computer. The measurement is performed by a special video analysis programme.

The tablet is characterized in that the volume of at least one of the layers increases, at the end of 2 hours, by 1.5 times and preferably by at least 3 times relative to the initial volume.

By this method, it is possible to study the behaviour "in vitro" of various preparations (described in the examples of the Application) and thus to design pharmaceutical preparations capable of satisfying the required morphological qualities, as well as of optimizing the preparation of each of the said layers so as to obtain the morphological behaviour which satisfies the requested aim. This type of analysis thus makes it possible to model the "in vivo" behaviour of the pharmaceutical preparation on contact with biological fluids. It is also possible to program, within a determined time period, the release of the active substance conveyed in the pharmaceutical preparation.

The pharmaceutical compositions of the present invention may be in the form of tablets or small tablets or gelatin capsules comprising small tablets.

At least two small tablets may also be combined in the same pharmaceutical composition. They may be packaged in a common envelope, for example in a wafer capsule or in a gelatin capsule.

When the pharmaceutical composition consists of small tablets, each of these may have a different or identical composition.

The examples which follow are intended to illustrate the invention.

EXAMPLE 1:

Preparation of a series of tablets (5000) based on alfuzosin hydrochloride.

1A: Preparation of the granulate containing the active substance

A granulate is prepared, according to the process described below, which is used for the preparation of the layer **2** of FIG. **1** containing 10.0 mg of alfuzosin hydrochloride and having the following unit composition:

Alfuzosin hydrochloride	10.00 mg
Mannitol	10.00 mg
Hydroxypropylmethylcellulose USP 2208	10.00 mg
Polyvinylpyrrolidone	3.20 mg
Microcrystalline cellulose	65.00 mg
Magnesium stearate	1.00 mg
Colloidal silica	1.25 mg
Total	100.45 mg

The manufacturing process consists in preparing a granulate by mixing together the amounts of active substance required, mannitol, microcrystalline cellulose and hydroxypropylmethylcellulose. The uniform powder mixture is moistened uniformly with an alcoholic solution based on 10% w/v polyvinyl-pyrrolidone and is then dried to a predetermined percentage of residual moisture in a fluidized-air bed at 40–45° C. The dried granulate is calibrated and placed in a powder mixer with magnesium stearate and colloidal silica and it is then mixed until homogeneous.

1B: Preparation of the granulate constituting layer 1 which swells

An amount of granulate required to obtain 5000 layers which swell, layer 1 of FIG. 1, were prepared, each layer having the following percentage composition:

Hydroxypropylmethylcellulose	79.75%
Hydrogenated castor oil	13.50%
Yellow iron oxide	0.25%
Ethylcellulose	5.00%
Magnesium stearate	1.00%
Silica gel	0.50%
Total	100.00%

The manufacturing process consists of the preparation of a granulate obtained by mixing the required amounts of hydroxypropylmethylcellulose, hydrogenated castor oil and iron oxide; the uniform powder mixture is moistened with an alcoholic solution based on 10% w/v ethylcellulose and the uniformly moistened mass is dried in a fluidized-air bed at 40–45° C. The granulate, dried to a predetermined percentage of moisture, is calibrated and placed in a powder mixer with magnesium stearate and colloidal silica and it is mixed until homogeneous.

1C: Preparation of the granulate constituting the third layer **3** which acts as a barrier

An amount of granulate required to obtain 5000 barrier layers is prepared, layer **3** of FIG. **1**, each layer having the following percentage composition:

Hydroxypropylmethylcellulose	76.00%
Hydrogenated castor oil	18.60%
Polyvinylpyrrolidone	3.15%
Yellow iron oxide	0.10%
Magnesium stearate	0.70%
Colloidal silica	1.45%
Total	100.00%

The manufacturing process consists in mixing the required amounts of hydroxypropylmethylcellulose, hydrogenated castor oil and yellow iron oxide; the homogeneous powder mixture is moistened with a solution based on 10% w/v polyvinylpyrrolidone in ethanol and the wet mass is dried in a fluidized-air bed at 40–45° C. The granulate, dried to a predetermined percentage of residual moisture, is calibrated and placed in a powder mixer with magnesium stearate and colloidal silica and mixed until homogeneous.

1D: Preparation of tablets containing three layers (by compression)

The granulates obtained are loaded into the three supply hoppers of a rotary multi-layer press capable of producing three-layer tablets. The granulate described in point 1B is loaded into the first hopper, the granulate according to the description of point 1A is loaded into the second hopper and the granulate according to the description of point 1C is loaded into the third hopper; granulates 1B and 1C may be inverted in the hoppers.

The multi-layer press is equipped with flat circular bevelled punches having a diameter of 8 mm. The machine is adjusted to produce three-layer tablets consisting of a first amount of 100 mg of layer 1 for a thickness of about 1.7 mm, a second amount of 100.45 mg of granulate containing the active substance (equivalent to 10.0 mg of alfuzosin hydrochloride) and a third amount of 150 mg of layer **3** for a thickness of about 3.3 mm. Working according to the above description, three-layer tablets having an average weight of 350.45 mg and containing 10.0 mg of alfuzosin hydrochloride are produced.

1E: Dissolution test

In order to evaluate the release properties of the complete tablets, the vane machine (described in USP XXIII) is used, working at 100 rpm and using as dissolution liquid a 0.01M HCl solution at 37° C. The release of the active substance is monitored by UV spectrophotometric determination at 330 nm using a sampling and automatic reading system.

The results of the tests carried out are given in Table 1.

TABLE 1

Time (hours)	% released
1	16.0
2	25.0
3	32.0
4	37.0
6	48.0
8	57.0
10	66.0
12	74.0
16	88.0

TABLE 1-continued

Time (hours)	% released
20	95.0
24	98.0

A controlled release of the active substance is obtained in about 20 hours.

1F: Swelling test

The test is carried out under the same experimental conditions as the dissolution test. The tablets are taken from the dissolution medium at regular intervals and their volume and the sizes of the various layers are measured with a video-microscope coupled to an image-analysis system. The results of the tests carried out are given in Table 2.

TABLE 2

Swelling time (hours)	Volume (layer 2 + layer 3) (%)	Volume of layer 1 (%)
0	100.0	100.0
0.5	142.0	211.1
1	152.7	271.0
1.5	175.2	302.6
2	161.8	399.5
3	182.7	483.7
4	196.0	534.0
5	199.4	609.8
6	195.7	727.9
7	166.8	809.9
8	138.9	851.0
10	139.9	937.5

It may be noted that, in the tablets, layer **1** increases considerably in volume, up to 9 times its initial volume. This phenomenon is very evident if it is related to the increase in volume of the other two layers, layer **2** and layer **3**, which cumulatively swell to about 2-fold. In addition, layer **1** increases in volume at a rate which is considerably higher than that of the other layers.

EXAMPLE 2

Preparation of a series of tablets (10,000) as reported in FIGS. **1** and **2**, containing alfuzosin hydrochloride as active substance.

2A: Preparation of the granulate containing the active substance

A granulate is prepared, according to the process described in Example 1A, which is used in the preparation of the layer **2** of FIG. **1** containing 7.5 mg of alfuzosin hydrochloride, and having the following unit composition:

Alfuzosin hydrochloride	7.50 mg
Mannitol	10.00 mg
Hydroxypropylmethylcellulose	10.00 mg
Polyvinylpyrrolidone	3.20 mg
Microcrystalline cellulose	65.00 mg
Magnesium stearate	1.00 mg
Colloidal silica	1.25 mg
Total	97.95 mg

2B: Preparation of the granulate constituting the first layer **1** which swells

An amount of granulate required to obtain 10,000 layers which swell, layer **1** of FIG. **1**, is prepared according to the process described in Example 1B, each layer having the following percentage unit composition:

Hydroxypropylmethylcellulose	79.75%
Hydrogenated castor oil	13.50%
Ethylcellulose	5.00%
Iron oxide	0.25%
Magnesium stearate	1.00%
Colloidal silica	0.50%
Total	100.00%

2C: Preparation of the granulate constituting the third layer **3**

An amount of granulate required to obtain 10,000 barrier layers, layer **3** of FIG. **1**, is prepared according to the process described in Example 1C, each layer having the following percentage unit composition:

Hydroxypropylmethylcellulose	76.00%
Hydrogenated castor oil	18.60%
Polyvinylpyrrolidone	3.15%
Yellow iron oxide	0.10%
Magnesium stearate	1.45%
Colloidal silica	0.70%
Total	100.00%

2D: Preparation of the three-layer tablets (by compression)

The granulates obtained according to Examples 2A, 2B and 2C are loaded into the three supply hoppers of a rotary press with respective amounts of 100 mg of granulate for layer **1** for a thickness of 1.75 mm, 97.95 mg of granulate containing the active substance (corresponding to 7.5 mg of alfuzosin hydrochloride) for layer **2** and 150 mg for layer **3** for a thickness of 3.3 mm. By working in the manner described above, three-layer tablets having an average weight of 347.95 mg and containing 7.5 mg of active substance are obtained.

2E: Dissolution test

The dissolution tests are carried out according to the process described in Example 1E.

The results are given in Table 3.

TABLE 3

Time (hours)	% released
1	15.1
2	24.4
4	37.7
6	48.0
8	57.6
10	66.0
12	74.2
14	82.2
16	89.1
18	94.8
20	98.6

It may be noted that the controlled release of the active substance takes place over about 20 hours.

2F: Swelling test

The swelling tests are carried out according to the process described in Example 1F. The results are given in Table 4.

TABLE 4

Time (hours)	Volume (layer 2 + layer 3) (%)	Volume of layer 1 (%)
0	100.0	100.0
0.5	137.6	233.2
1	142.3	305.1
1.5	150.4	338.5
2	142.3	412.4
3	167.1	435.2
4	139.2	526.5
6	132.0	665.0
8	129.9	715.1

It may be noted that in the tablets prepared, the volume of layer **1** increases considerably, by up to 7 times the initial volume; layer **2** and layer **3** increase by up to one and a half times. In addition, layer **1** increases in volume at a rate which is very much higher than that of the other two layers.

EXAMPLE 3

Preparation of a series of tablets (10,000) containing alfuzosin hydrochloride as active substance

3A: Preparation of the granulate containing the active substance.

A granulate used in the preparation of layer **2** is prepared according to the process described in Example 1A, this granulate containing 10.0 mg of alfuzosin hydrochloride and having the following unit composition:

Alfuzosin hydrochloride	10.00 mg
Mannitol	10.00 mg
Hydroxypropylmethylcellulose	10.00 mg
Polyvinylpyrrolidone	3.20 mg
Microcrystalline cellulose	65.00 mg
Magnesium stearate	1.00 mg
Colloidal silica	1.25 mg
Total	100.45 mg

3B: Preparation of the granulate constituting the first layer **1** which swells

An amount of granulate required to obtain 10,000 layers which swell, layer **1** of FIG. **1**, is prepared according to the process described, each layer having the following percentage composition:

Hydroxypropylmethylcellulose	75.00%
Glyceryl behenate	13.40%
Polyvinylpyrrolidone	5.00%
Iron oxide	0.10%
Polyvinylpyrrolidone	5.00%
Magnesium stearate	1.00%
Colloidal silica	0.50%
Total	100.00%

3C: Preparation of the granulate constituting the third layer **3**

An amount of granulate required to obtain 10,000 layers, layer **3** of FIG. **1**, is prepared according to the process described in Example 1C, each layer having the following percentage composition:

Hydroxypropylmethylcellulose	76.00%
Hydrogenated castor oil	18.60%
Polyvinylpyrrolidone	3.15%
Yellow iron oxide	0.10%
Magnesium stearate	1.45%
Colloidal silica	0.70%
Total	100.00%

3D: Preparation of three-layer tablets (by compression)

The granulates obtained as described in Examples 3A, 3B and 3C are loaded into the three supply hoppers of a rotary press with respective amounts of 100 mg of granulate for layer **1**, 100.45 mg of granulate containing the active substance for layer **2** and 150 mg for layer **3**. By working in the manner described above, three-layer tablets having an average weight of 350.45 mg and containing 10.0 mg of active substance are obtained.

3E: Dissolution test

The dissolution tests are carried out according to the process described in Example 1E.

The results of the tests carried out are given in Table 5.

TABLE 5

Time (hours)	% released
1	19.0
2	27.8
4	41.7
6	53.4
8	64.7
10	75.6
12	84.6
14	90.9
16	95.1
18	97.8
20	99.4

The controlled release of the active substance takes place over about 18 hours.

3F: Swelling test

The swelling tests are carried out according to the process described in Example 1F.

The results of the tests carried out are given in Table 6.

TABLE 6

Time (hours)	Volume (layer 2 + layer 3) (%)	Volume of layer 1 (%)
0	100.0	100.0
0.5	124.0	231.8
1	130.5	297.0
2	108.5	387.0
3	115.2	448.8
4	131.3	517.2
5	124.7	554.5
6	137.0	601.1
8	106.6	740.5

It may be noted that in the tablets prepared, the volume of layer **1** which swells increases considerably, by up to 7 times its initial volume; layer **2** and layer **3** only increase by 30–40% relative to the initial volume. In addition, the layer which swells increases in volume at a rate which is very much higher than that of the other two layers.

EXAMPLE 4

Preparation of a series of tablets (5000) based on alfuzosin hydrochloride.

4A: Preparation of the granulate containing the active substance

A granulate is prepared according to the process described below, which is used for the preparation of layer 2 of FIG. 1 containing 10.0 mg of alfuzosin hydrochloride and having the following unit composition:

Alfuzosin hydrochloride	10.00 mg
Lactose	60.30 mg
Hydroxypropylmethylcellulose USP 2208	25.00 mg
Polyvinylpyrrolidone	3.20 mg
Magnesium stearate	1.00 mg
Colloidal silica	0.50 mg
Total	100.00 mg

The manufacturing process consists in preparing a granulate by mixing the required amounts of active substance, of lactose, of polyvinylpyrrolidone and of hydroxypropylmethylcellulose. The uniform powder mixture is uniformly moistened with purified water and is then dried to a predetermined residual moisture percentage in a fluidized-air bed at 40–45° C. The dried granulate is calibrated and placed in a powder mixer with magnesium stearate and colloidal silica and is then mixed until homogeneous.

4B: Preparation of the granulate constituting layers 1 and 3 which swell and form a barrier

An amount of granulate required to obtain 10,000 layers which swell and form a barrier, layers 1 and 3 of FIG. 1, is prepared, each layer having the following percentage composition:

Hydroxypropylmethylcellulose USP 2208	40.00%
Lactose	39.75%
Glyceryl behenate	13.50%
Yellow iron oxide	0.25%
Polyvinylpyrrolidone	5.00%
Magnesium stearate	1.00%
Colloidal silica	0.50%
Total	100.00%

The manufacturing process consists in preparing a granulate obtained by mixing together the required amounts of hydroxypropylmethylcellulose, of lactose, of glyceryl behenate, of polyvinylpyrrolidone and of iron oxide; the uniform powder mixture is moistened with purified water. The uniformly moistened mass is dried in a fluidized-air bed at 40–45° C. The granulate, dried to a predetermined moisture percentage, is calibrated and placed in a powder mixer with magnesium stearate and colloidal silica and it is mixed until homogeneous.

4C: Preparation of three-layer tablets (by compression)

The granulates obtained are loaded into the three supply hoppers of a rotary multilayer press capable of producing three-layer tablets. The granulate described in point 4B is loaded into the first and third hoppers; the granulate according to the description of point 4A is loaded into the second hopper.

The multi-layer press is equipped with flat circular bevelled punches having a diameter of 8 mm. The machine is adjusted to produce three-layer tablets consisting of a first amount of 100 mg of layer 1 or 3 for a thickness of about 1.7 mm, a second amount of 100 mg of granulate containing the active substance and a third amount of 100 mg of layer 1 or 3 for a thickness of about 1.7 mm. By working according to the above description, three-layer tablets having an average weight of 300 mg and containing 10.0 mg of alfuzosin hydrochloride are produced.

EXAMPLE 5

Preparation of a series of tablets (5000) based on alfuzosin hydrochloride.

5A: Preparation of the granulate containing the active substance

A granulate is prepared according to the process described in Example 4A, this granulate being used in the preparation of layer 2 of FIG. 1 containing 15 mg of alfuzosin hydrochloride and having the following unit composition:

Alfuzosin hydrochloride	15.00 mg
Lactose	55.30 mg
Hydroxypropylmethylcellulose USP 2208	25.00 mg
Polyvinylpyrrolidone	3.20 mg
Magnesium stearate	1.00 mg
Colloidal silica	0.50 mg
Total	100.00 mg

5B: Preparation of the granulate constituting layers 1 and 3 which swell and form a barrier

An amount of granulate required to obtain 10,000 layers which swell and form a barrier, layers 1 and 3 of FIG. 1, is prepared, each layer corresponding to the composition and to the manufacturing process described in Example 4B.

5C: Preparation of three-layer tablets (by compression)

By working in the manner described above (Example 4C), three-layer tablets containing 15.0 mg of active substance are obtained with the granulates described in Examples 5A and 5B.

EXAMPLE 6

Preparation of a series of tablets (5000) based on alfuzosin hydrochloride.

6A: Preparation of the granulate containing the active substance

A granulate is prepared according to the process described below, this granulate being used in the preparation of layer 2 of FIG. 1 containing 10 mg of alfuzosin hydrochloride and having the following unit composition:

Alfuzosin hydrochloride	10.00 mg
Microcrystalline cellulose	33.80 mg
Mannitol	10.00 mg
Hydroxypropylmethylcellulose USP 2208	40.00 mg
Polyvinylpyrrolidone	5.00 mg
Magnesium stearate	1.00 mg
Colloidal silica	0.20 mg
Total	100.00 mg

The manufacturing process consists in preparing a granulate by mixing together the required amounts of active substance, of cellulose, of polyvinylpyrrolidone, of mannitol and of hydroxypropylmethylcellulose. The uniform powder mixture is moistened uniformly with purified water and is then dried to a predetermined residual moisture percentage in a fluidized-air bed at 40–50° C. The dried granulate is

calibrated and placed in a powder mixer with magnesium stearate and colloidal silica until homogeneous.

6B: Preparation of the granulate constituting layers 1 and 3 which swell and form a barrier

An amount of granulate required to obtain 10,000 layers which swell and form a barrier, layers 1 and 3 of FIG. 1, is prepared, each layer having the following percentage composition:

Hydroxypropylmethylcellulose USP 2208	45.00%
Lactose	28.60%
Microcrystalline cellulose	20.00%
Yellow iron oxide	0.20%
Polyvinylpyrrolidone	5.00%
Magnesium stearate	1.00%
Colloidal silica	0.20%
Total	100.00%

The manufacturing process is identical to that of Example 4B, the microcrystalline cellulose being added in place of the glyceryl behenate.

6C: Preparation of three-layer tablets (by compression)

By working in the manner described above (Example 4C), three-layer tablets containing 10.0 mg of active substance are obtained with 100 mg, for each of the layers, of granulates described in Examples 6A and 6B, layers 1 and 3 having a thickness of about 1.8 mm.

EXAMPLE 7

Preparation of a series of tablets (5000) based on alfuzosin hydrochloride.

7A: Preparation of the granulate containing the active substance

A granulate is prepared according to the process described below, this granulate being used in the preparation of layer 2 of FIG. 1 containing 15 mg of alfuzosin hydrochloride and having the following unti composition:

Alfuzosin hydrochloride	15.00 mg
Microcrystalline cellulose	28.80 mg
Mannitol	10.00 mg
Hydroxypropylmethylcellulose USP 2208	40.00 mg
Polyvinylpyrrolidone	5.00 mg
Magnesium stearate	1.00 mg
Colloidal silica	0.20 mg
Total	100.00 mg

The manufacturing process is identical to that of Example 6A.

7B: Preparation of the granulate constituting layers 1 and 3 which swell and form a barrier

An amount of granulate required to obtain 10,000 layers which swell and form a barrier, layers 1 and 3 of FIG. 1, is prepared, each layer corresponding to the composition and to the manufacturing process described in Example 6B.

7C: Preparation of three-layer tablets (by compression)

By working in the manner described above (Example 6C), three-layer tablets containing 15.0 mg of active substance are obtained with the granulates described in Examples 7A and 7B.

EXAMPLE 8

Preparation of a series of tablets (5000) based on alfuzosin hydrochloride.

8A: Preparation of the granulate containing the active substance

A granulate is prepared, which is used in the preparation of layer 2 of FIG. 1, containing 10 mg of alfuzosin hydrochloride, with a composition identical to that described in Example 6A and according to the same process.

8B: Preparation of the granulate constituting layers 1 and 3 which swell and form a barrier

An amount of granulate required to obtain 10,000 layers which swell and form a barrier, layers 1 and 3 of FIG. 1, is prepared, each layer having the following percentage composition:

Hydroxypropylmethylcellulose USP 2208	35.00%
Lactose	34.50%
Microcrystalline cellulose	23.90%
Yellow iron oxide	0.40%
Polyvinylpyrrolidone	5.00%
Magnesium stearate	1.00%
Colloidal silica	0.20%
Total	100.00%

The manufacturing process is identical to that of Example 6B.

8C: Preparation of three-layer tablets (by compression)

The granulates obtained are loaded into the three supply hoppers of a rotary multi-layer press capable of producing three-layer tablets. The granulate described in point 8B is loaded into the first and third hoppers; the granulate according to the description of point 8A is loaded into the second hopper.

The multi-layer press is equipped with flat circular bevelled punches having a diameter of 8 mm. The machine is adjusted to produce three-layer tablets whose outer layers consist of 100 mg and 150 mg of the granulate described in point 8B and corresponding respectively to a thickness of about 1.7 mm for one of them and 2.7 mm for the other. The inner layer is composed of 100 mg of granulate containing the active substance (equivalent to 10.0 mg of alfuzosin hydrochloride). By working according to the above description in point 7C, three-layer tablets having an average weight of 350 mg and containing 10.0 mg of alfuzosin hydrochloride are produced.

EXAMPLE 9

Preparation of a series of tablets (5000) based on alfuzosin hydrochloride.

9A: Preparation of the granulate containing the active substance

A granulate is prepared, which is used in the preparation of layer 2 of FIG. 1, containing 15 mg of alfuzosin hydrochloride, with a composition identical to that described in Example 7A and according to the same process.

9B: Preparation of the granulate constituting layers 1 and 3 which swell and form a barrier

An amount of granulate required to obtain 10,000 layers which swell and form a barrier, layers 1 and 3 of FIG. 1, is prepared, each layer corresponding to the composition and to the manufacturing process described in Example 8B.

9C: Preparation of the three-layer tablets (by compression)

By working in the manner described above (Example 8C), three-layer tablets containing 15.0 mg of active substance

and having an average weight of 350 mg are obtained with 100 mg of granulate described in Example 9A and, for the outer layers, 100 and 150 mg of granulate described in point 9B corresponding respectively to a thickness of about 1.8 mm for one and 2.7 mm for the other.

EXAMPLE 10

Preparation of a series of tablets (5000) based on alfuzosin hydrochloride.

10A: Preparation of the granulate containing the active substance

A granulate is prepared, which is used in the preparation of layer **2** of FIG. **1**, containing 7.5 mg of alfuzosin hydrochloride, with a composition which is identical to that described in Example 2A and according to the same process.

10B: Preparation of the granulate constituting layers **1** and **3** which swell and form a barrier

An amount of granulate required to obtain 10,000 layers which swell and form a barrier, layers **1** and **3** of FIG. **1**, is prepared, each layer corresponding to the composition and to the manufacturing process described in Example 4B.

10C: Preparation of the three-layer tablets (by compression)

By working in the manner described above (Example 8C), three-layer tablets containing 7.5 mg of active substance and having an average weight of 350 mg are obtained, with 100 mg of granulate described in Example 10A and, for the outer layers, 100 and 150 mg of granulate described in point 10B, corresponding respectively to a thickness of about 1.8 mm for one and 5 2.7 mm for the other.

EXAMPLE 11

Preparation of a series of tablets (5000) based on alfuzosin hydrochloride.

11A: Preparation of the granulate containing the active substance

A granulate containing 10 mg of alfuzosin hydrochloride is prepared, with a composition which is identical to that described in Example 4A and according to the same process.

11B: Preparation of the granulate constituting layer **1** which swells

An amount of granulate required to obtain 10,000 layers which swell is prepared. Each layer corresponds to the composition and to the manufacturing process described in Example 4B.

11C: Preparation of the two-layer tablets (by compression)

By working in the manner described above (Example 8C), the granulates obtained, 100 mg of granulate described in Example 10A and, for the outer layer, 150 mg of granulate described in point 10B, are loaded into two supply hoppers of a rotary multi-layer press capable of producing two-layer tablets.

What is claimed is:

1. A pharmaceutical tablet for oral administration and for the controlled release of alfuzosin hydrochloride into the proximal segments of the gastrointestinal tract, the tablet comprising:

a) a first layer having the property of swelling considerably and quickly on contact with aqueous biological fluids, the first layer being produced by compression of a mixture or of a granulate comprising a hydrophilic polymer constituting from 5.0 to 90% of the weight of the first layer,

b) a second layer adjacent to the first layer containing the alfuzosin hydrochloride, the second layer being formulated with a hydrophilic polymer and with an auxiliary substance to give the preparation suitable properties of compressibility and in order to allow the release of alfuzosin hydrochloride within a predetermined time period,

c) and optionally a third layer adjacent to the second layer comprising a hydrophilic polymer which gels and/or swells and which may optionally be broken down and has a barrier function which modifies the release of the alfuzosin hydrochloride from the second layer, the third layer being primarily highly impervious to passage of the active substance.

2. The tablet according to claim **1**, wherein at least one of the layers comprises an hydrophilic product and/or an excipient.

3. The tablet according to claim **2**, wherein the hydrophilic excipient is crosslinked polyvinylpyrrolidone, hydroxypropylcellulose or hydroxypropylmethylcellulose having a molecular weight from 1,000 to 100,000, crosslinked sodium carboxymethylcellulose, carboxymethyl starch or its salts, or divinylbenzene/potassium methyacrylate copolymer.

4. The tablet according to claim **2**, wherein the hydrophilic excipient constitutes from 1 to 50% of the weight of the layer.

5. The tablet according to claim **1**, wherein the third layer has an identical composition to that of the first layer and the same functional properties.

6. The tablet according to claim **5**, wherein the first and third layers differ in the amount applied to the second layer and their thickness.

7. The tablet according to claim **1**, wherein, on contact with an aqueous liquid, at least one of the layers of the tablet increases by at least 1.5 times relative to the initial volume after two hours.

8. Tablet according to claim **1**, wherein the hydrophilic polymer is hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose having a molecular weight of from 1000 to 4,000,000, hydroxypropylcellulose having a molecular weight of from 2000 to 2,000,000, a carboxyvinyl polymer, a chitosan, a mannan, a galactomannan, a xanthan, a carrageenan, an amylose, an alginic acid, a pectin, an acrylate, a methacrylate, an acrylic/methacrylic copolymer, a polyanhydride, a polyamino acid, a poly(methyl vinyl ether/maleic anhydride) polymer, a polyvinyl alcohol, a glucan, a scleroglucan, a carboxymethylcellulose, an ethylcellulose, or a methylcellulose.

9. The tablet according to claim **1**, wherein the second layer containing the active substance comprises 5 to 90% by weight of the hydrophilic polymer.

10. The tablet according to claim **1**, wherein the third layer contains alfuzosin hydrochloride.

11. The tablet according to claim **1**, wherein the amount of alfuzosin hydrochloride in the tablet ranges from 2.5 to 50 mg.

12. The tablet according to claim **1**, further comprising a surfactant which is sodium lauryl, sulphate, sodium ricinoleate, sodium tetradecyl sulphate, sodium dioctyl, sulphosuccinate, cetomacrogol, poloxamer, glyceryl monostearate, a polysorbate, sorbitan monolaurate, or a lecithin.

13. The tablet according to claim **1**, further comprising an hydrophilic diluent which is mannitol, lactose, a starch, sorbitol, xylitol, microcrystalline cellulose or a substance which promotes the penetration of water and/or an aqueous fluid into the layers.

14. The tablet according to claim **1**, further comprising an hydrophobic diluent which is glyceryl monostearate, a palmitate, an hydrogenated plant oil or a wax used for

slowing down the penetration of water and/or of aqueous fluids into the second layer containing the active substance and into the first and third layers.

15. The tablet according to claim **1**, wherein the layers of the tablet have different thicknesses ranging from 0.2 mm to 8 mm.

16. The tablet according to claim **1**, wherein the tablet is compressed at a pressure that ranges from 7 to 50 KN.

17. The tablet according to claim **1**, wherein the tablet is covered with a coating which may optionally contain alfuzosin hydrochloride.

18. A pharmaceutical composition comprising one or more tablets according to claim **1**.

19. The tablet according to claim **1**, wherein the hydrophilic polymer constitutes from 10 to 85% of the weight of the first layer.

20. The tablet according to claim **2**, wherein the hydrophilic excipient constitutes from 10 to 30% of the weight of the layer.

21. The tablet according to claim **1**, wherein, on contact with an aqueous liquid, at least one of the layers of the tablet increases by at least 3 times relative to the initial volume after two hours.

22. The tablet according to claim **1**, wherein the second layer comprises 10 to 85% by weight of the hydrophilic polymer.

23. The tablet according to claim 1, wherein

a) the first layer consists of by weight:

hydroxypropylmethylcellulose	79.75%
hydrogenated castor oil	13.50%
yellow iron oxide	0.25%
ethylcellulose	5.00%
magnesium stearate	1.00%
silica gel	0.50%

b) the second layer consists of by weight:

alfuzosin hydrochloride	10.00 mg
mannitol	10.00 mg
hydroxypropylmethylcellulose	10.00 mg
polyvinylpyrrolidone	3.20 mg
microcrystalline cellulose	65.00 mg
magnesium stearate	1.00 mg
colloidal silica	1.25 mg

c) and the third layer consists of by weight:

hydroxypropylmethylcellulose	76.00%
hydrogenated castor oil	18.60%
polyvinylpyrrolidone	3.15%
yellow iron oxide	0.10%
magnesium stearate	0.70%
colloidal silica	1.45%.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,149,940
DATED : November 21, 2000
INVENTOR(S) : Maggi et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [73], correct the name of the Assignee from "**Jagotec AB**" to -- **Jagotec AG** --.

Signed and Sealed this

Thirtieth Day of April, 2002

Attest:

Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

JS 44 (Rev. 11/04)

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON THE REVERSE OF THE FORM.)

I. (a) PLAINTIFFS
sanofi-aventis and
sanofi-aventis U.S. LLC

DEFENDANTS
Actavis South Atlantic LLC, et al.

(b) County of Residence of First Listed Plaintiff _____
(EXCEPT IN U.S. PLAINTIFF CASES)

County of Residence of First Listed Defendant _____
(IN U.S. PLAINTIFF CASES ONLY)
NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE LAND INVOLVED.

(c) Attorney's (Firm Name, Address, and Telephone Number)
Jack B. Blumenfeld, MORRIS, NICHOLS, ARSHT & TUNNELL LLP,
1201 North Market Street, P.O. Box 1347,
Wilmington, DE 19899-1347, (302) 658-9200

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
- ☒ 3 Federal Question (U.S. Government Not a Party)
- ☐ 2 U.S. Government Defendant
- ☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)
(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT (Place an "X" in One Box Only)

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excl. Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury

PERSONAL INJURY
- ☐ 362 Personal Injury - Med. Malpractice
- ☐ 365 Personal Injury - Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 444 Welfare
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 440 Other Civil Rights

PRISONER PETITIONS
- ☐ 510 Motions to Vacate Sentence

Habeas Corpus:
- ☐ 530 General
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

FORFEITURE/PENALTY
- ☐ 610 Agriculture
- ☐ 620 Other Food & Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 R.R. & Truck
- ☐ 650 Airline Regs.
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Mgmt. Relations
- ☐ 730 Labor/Mgmt.Reporting & Disclosure Act
- ☐ 740 Railway Labor Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Empl. Ret. Inc. Security Act

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☒ 830 Patent
- ☐ 840 Trademark

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Sat TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☐ 895 Freedom of Information Act
- ☐ 900Appeal of Fee Determination Under Equal Access to Justice
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN (Place an "X" in One Box Only)

☒ 1 Original Proceeding ☐ 2 Removed from State Court ☐ 3 Remanded from Appellate Court ☐ 4 Reinstated or Reopened ☐ 5 Transferred from another district (specify) ☐ 6 Multidistrict Litigation ☐ 7 Appeal to District Judge from Magistrate Judgment

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing **(Do not cite jurisdictional statutes unless diversity)**:
35 U.S.C. Section 271

Brief description of cause:
Patent infringement

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23

DEMAND $

CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY

(See instructions): ~~JUDGE~~ sanofi-aventis, et al. v. Barr Laboratories, Inc. being filed simultaneously with this action. ~~DOCKET NUMBER~~

DATE September 21, 2007

SIGNATURE OF ATTORNEY OF RECORD Jack B. Blumenfeld

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

INSTRUCTIONS FOR ATTORNEYS COMPLETING CIVIL COVER SHEET FORM JS 44

Authority For Civil Cover Sheet

The JS 44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleading or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. The attorney filing a case should complete the form as follows:

I. (a) Plaintiffs-Defendants. Enter names (last, first, middle initial) of plaintiff and defendant. If the plaintiff or defendant is a government agency, use only the full name or standard abbreviations. If the plaintiff or defendant is an official within a government agency, identify first the agency and then the official, giving both name and title.

(b) County of Residence. For each civil case filed, except U.S. plaintiff cases, enter the name of the county where the first listed plaintiff resides at the time of filing. In U.S. plaintiff cases, enter the name of the county in which the first listed defendant resides at the time of filing. (NOTE: In land condemnation cases, the county of residence of the "defendant" is the location of the tract of land involved.)

(c) Attorneys. Enter the firm name, address, telephone number, and attorney of record. If there are several attorneys, list them on an attachment, noting in this section "(see attachment)".

II. Jurisdiction. The basis of jurisdiction is set forth under Rule 8(a), F.R.C.P., which requires that jurisdictions be shown in pleadings. Place an "X" in one of the boxes. If there is more than one basis of jurisdiction, precedence is given in the order shown below.

United States plaintiff. (1) Jurisdiction based on 28 U.S.C. 1345 and 1348. Suits by agencies and officers of the United States are included here.

United States defendant. (2) When the plaintiff is suing the United States, its officers or agencies, place an "X" in this box.

Federal question. (3) This refers to suits under 28 U.S.C. 1331, where jurisdiction arises under the Constitution of the United States, an amendment to the Constitution, an act of Congress or a treaty of the United States. In cases where the U.S. is a party, the U.S. plaintiff or defendant code takes precedence, and box 1 or 2 should be marked.

Diversity of citizenship. (4) This refers to suits under 28 U.S.C. 1332, where parties are citizens of different states. When Box 4 is checked, the citizenship of the different parties must be checked. (See Section III below; federal question actions take precedence over diversity cases.)

III. Residence (citizenship) of Principal Parties. This section of the JS 44 is to be completed if diversity of citizenship was indicated above. Mark this section for each principal party.

IV. Nature of Suit. Place an "X" in the appropriate box. If the nature of suit cannot be determined, be sure the cause of action, in Section VI below, is sufficient to enable the deputy clerk or the statistical clerks in the Administrative Office to determine the nature of suit. If the cause fits more than one nature of suit, select the most definitive.

V. Origin. Place an "X" in one of the seven boxes.

Original Proceedings. (1) Cases which originate in the United States district courts.

Removed from State Court. (2) Proceedings initiated in state courts may be removed to the district courts under Title 28 U.S.C., Section 1441. When the petition for removal is granted, check this box.

Remanded from Appellate Court. (3) Check this box for cases remanded to the district court for further action. Use the date of remand as the filing date.

Reinstated or Reopened. (4) Check this box for cases reinstated or reopened in the district court. Use the reopening date as the filing date.

Transferred from Another District. (5) For cases transferred under Title 28 U.S.C. Section 1404(a). Do not use this for within district transfers or multidistrict litigation transfers.

Multidistrict Litigation. (6) Check this box when a multidistrict case is transferred into the district under authority of Title 28 U.S.C. Section 1407. When this box is checked, do not check (5) above.

Appeal to District Judge from Magistrate Judgment. (7) Check this box for an appeal from a magistrate judge's decision.

VI. Cause of Action. Report the civil statute directly related to the cause of action and give a brief description of the cause. **Do not cite jurisdictional statutes unless diversity.** Example: U.S. Civil Statute: 47 USC 553
Brief Description: Unauthorized reception of cable service

VII. Requested in Complaint. Class Action. Place an "X" in this box if you are filing a class action under Rule 23, F.R.Cv.P.

Demand. In this space enter the dollar amount (in thousands of dollars) being demanded or indicate other demand such as a preliminary injunction.

Jury Demand. Check the appropriate box to indicate whether or not a jury is being demanded.

VIII. Related Cases. This section of the JS 44 is used to reference related pending cases if any. If there are related pending cases, insert the docket numbers and the corresponding judge names for such cases.

Date and Attorney Signature. Date and sign the civil cover sheet.

AO FORM 85 RECEIPT (REV. 9/04)

United States District Court for the District of Delaware

Civil Action No. 07-572

ACKNOWLEDGMENT OF RECEIPT FOR AO FORM 85

NOTICE OF AVAILABILITY OF A UNITED STATES MAGISTRATE JUDGE TO EXERCISE JURISDICTION

I HEREBY ACKNOWLEDGE RECEIPT OF 2 COPIES OF AO FORM 85.

9/21/07
(Date forms issued)

X
(Signature of Party or their Representative)

X Aaron Johnston
(Printed name of Party or their Representative)

Note: Completed receipt will be filed in the Civil Action